Immunity
Letters

Characteristics of IL-17-Producing γδ T Cells

Rebecca O'Brien,[1,*] Niyun Jin,[1] Yafei Huang,[1] M. Kemal Aydintug,[1] Christina Roark,[1,2] and Willi Born[1]
[1]Integrated Department of Immunology, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA
[2]Beacon Biotechnology, Aurora, CO 80045, USA
*Correspondence: obrienr@njhealth.org
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In the August 2009 issue of *Immunity* (volume *31*, number 2), we read with great interest two articles that were written by Martin et al. (2009) and Sutton et al. (2009) and that focused on interleukin-17 (IL-17)-producing γδ T cells. We were, however, surprised to find that both of these papers claim priority for showing that γδ T cells can produce IL-17 without deliberate stimulation via the T cell receptor (TCR). We feel that this claim is unwarranted because in fact at least two previously published papers also arrived at this conclusion (but were not quoted by the authors of either of these *Immunity* papers). First, Shibata et al. (2007) showed by intracellular cytokine staining that ~50% of peritoneal cells from naive mice, when cultured with recombinant IL-23 only in vitro for 7 hr, produce IL-17. Second, Cheng et al. (2008) found that γδ T cells purified from mice immunized with a retinal protein-derived peptide, when cultured with a mixture of IL-1, IL-7, and IL-23 but without antigen, were likewise stimulated to produce IL-17.

Furthermore, both papers run into difficulties when they attempt to determine which subset of γδ T cells is responding in their systems by looking at expressed TCR elements among the IL-17-producing γδ T cells. Sutton et al. claim to have examined "Vγ4 and Vγ5" expression. Although it makes sense to look for Vγ4$^+$ γδ T cells, because they were found to almost exclusively represent the IL-17-producing population in the draining lymph nodes of mice with collagen-induced arthritis (Roark et al., 2007) and Sutton et al. indeed refer to this work, it really does not makes sense to look for Vγ5+ cells, which are observed only in the murine epidermis both normally and during inflammation. The cells examined by Sutton et al. were instead probably the Vγ7+ population because they found that more than 30% of the γδ T cells infiltrating the brains of mice with EAE, and 17% of those in spleen, expressed this Vγ chain. The apparent confusion here probably stems from the fact that this subset is also known as "Vγ5" by an alternate nomenclature (Garman et al., 1986), even though Sutton et al. refer to the other subset as "Vγ4" in accordance with the nomenclature of Heilig and Tonegawa (1986). Sutton et al. also look for expression of Vδ6.3 in the IL-17$^+$ γδ T cells, but do not explain why they did not instead look for Vδ4, which would have been the logical choice because virtually all of the Vγ4$^+$ cells producing IL-17 in the collagen-induced arthritis model coexpressed Vδ4. In the paper by Martin et al. (which uses the alternate nomenclature [Garman et al., 1986]), a potentially more serious mistake is made: the authors use two different models to examine γδ T cells; in both, the mice are injected with complete Freund's adjuvant (IFA plus heat-killed mycobacteria), but sometimes by a subcutaneous and sometimes by an intraperitoneal route. Our recent experiments show that different modes of immunization with CFA give rise to predominant IL-17 responses by completely different γδ T cell subsets. Whereas the intradermal route of immunization (and probably also the subcutaneous route used by Martin et al.) preferentially stimulates a Vγ4Vδ4$^+$ subset having well-defined TCR junctional motifs (Roark et al., 2007 and Figure S1A available online), the intraperitoneal route mainly expands γδ T cells with a different TCR (Figure S1B). Because TCR-defined γδ T cells subsets often differ functionally from one another (O'Brien et al., 2007), Martin et al. were thus probably comparing apples with oranges in their study.

Finally, with regard to the question of whether γδ T cells require prior TCR stimulation to produce IL-17, the authors do not appear to have considered the possibility that the responding γδ T cells in their systems may have already encountered a ligand and would not have responded in vitro to cytokines only were it not for that. If ligands for γδ T cells are, as is commonly speculated, stress-induced host molecules, they could well already have encountered a ligand. In the study by Shibata et al. (2007), γδ T cells from naive mice instead were used for examining this question, implying that TCR stimulation is indeed not necessary. However, as noted in Martin et al. (2009), normal peritoneal Vγ6Vδ1$^+$ γδ T cells show very high expression of CD44, which may mean they have been previously TCR-stimulated in some way and then recruited to the peritoneum. If these were CD4$^+$ αβ T cells, it would probably have been assumed that such cells represent preactivated or memory cells.

SUPPLEMENTAL INFORMATION

Supplemental Information includes one figure and can be found with this article online at doi:10.1016/j.immuni.2010.01.006.

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